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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
VIVLEMORE, TRACY ANN	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/701,236	BAKER ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-67* is/are pending in the application.

4a) Of the above claim(s) *11,13-24,26,27,36 and 38-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12,25,28-35,37 and 53-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *see box 6*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: IDS of 1/5/04, 4/5/04, 4/30/04, 8/11/04, 9/13/04, 12/9/04, 1/26/05, 3/14/05, 3/18/05, 4/4/05 and 4/15/05.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group I and the further election of invention I, claims 12 and 37, in the reply filed on July 17, 2006 is acknowledged. The traversal is on the ground(s) that inventions I and m, directed to the sugar surrogates of 4'-thioribonucleoside and 2'-deoxy-4'-thioribonucleoside, respectively are sufficiently similar that there would be no burden in searching both of these inventions. Applicant's arguments are found persuasive and invention m will be searched with the elected invention. Applicant has not provided arguments traversing the restriction between the elected invention and inventions a-k and n-p, therefore the election of invention I is presumed to be without traverse with regard to these inventions.

The requirement is still deemed proper and is therefore made FINAL.

Claims 11, 13-24, 26, 27, 36 and 38-52 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on July 17, 2006.

Claims 1-10, 12, 25, 28-35, 37 and 53-67 are examined on the merits. It is noted that the claim amendment of July 17, 2006 indicates claims 12, 25 and 37 as withdrawn. Claims 12 and 37 are part of the elected invention while claim 25 depends from claim 12 and is therefore also part of the elected invention and are not withdrawn. Any future amendments must properly reflect the status of the elected claims.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The claims of the instant application are directed to compositions comprising two chemically synthesized oligomers that are at least partially complementary and comprises at least one 4'-thionucleoside wherein one of the oligomers is capable of hybridizing with a target nucleic acid. Application 10/078,949 is directed to oligomeric compounds that hybridize to a target nucleic acid. This application does not provide support for compositions comprising two chemically synthesized oligomers that are at least partially complementary. Therefore, the priority date accorded this application is November 5, 2002, the filing date of application 60/423,760. If applicant believes 10/078,949 provides support for the instantly claimed invention it should be pointed out with particularity in any response to this action.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-10, 12, 25, 28-35, 37 and 53-58 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 24 of copending Application No. 10/700,697. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are directed to compositions of oligomers comprising 4'-thionucleosides while claim 24 of the '697 application is directed to an composition of two oligomers that comprises at least one nucleoside having a 3' endo sugar conformation wherein that nucleoside is a 2'-deoxy-4'-thioribonucleoside. Although the instant specification does not recite that 4'-thionucleosides have 3' endo sugar conformations, the claims of the '697 application are an obvious variant of the instant claims because they are directed to compositions that comprise the identical nucleotide modification and the disclosure of the '697 application provides support for compositions comprising RISC and oligomeric compounds comprising a single nucleic acid strand having self-complementarity.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Objections

Claims 12 and 37 are objected to because of the following informalities: each of these claims contains non-elected subject matter, specifically the non-elected sugar surrogates. Appropriate correction is required.

Claims 12, 25 and 37 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 1 and 28 have been amended to recite compositions of oligomers that comprise at least one 4'-thionucleoside. Because each of claims 12, 25 and 37 recite a 4'-thionucleoside as a limitation, these claims do not further limit the subject matter of the claims from which they depend.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-35, 37 and 62-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 28-35 and 37 are directed to compositions comprising an oligomer having a 4'-thionucleoside and a protein that comprises at least a portion of a RNA-induced silencing complex (RISC).

The specification describes RISC as being a ribonucleoprotein complex that contains an oligonucleotide and proteins of the Argonaute family, among others. The specification further discloses eIF2C1 and eIF2C2 as exemplary Argonaute proteins.

The art teaches that prior to and even after the time of filing the precise size and composition of a RISC complex has not been fully elucidated for any species even though several proteins such as those in the Argonaute family have been identified as components of RISC. See, for example, Meister et al. (Nature 2004), and Martinez et al. (Cell 2002, cited on IDS of 4/5/04).

Martinez et al. describe on pages 566-568 the partial purification of human RISC and identify two proteins, eIF2C1 and eIF2C2/GERp95 as components. Martinez et al. note on page 568 that other proteins present in human RISC are yet to be identified.

Meister et al. describe the state of the art with regard to the RISC of several species in late 2004. At page 344 Meister teaches that several forms of RISC differing in size and composition have been reported. At column 2 of this page the differences in mass of various RISCs are attributed to weak and/or transient association of proteins involved in initial processing of dsRNA and to "factors of unknown function". At page 346, second column Meister et al. teach that while it is known that RISC complexes catalyze hydrolysis of phosphodiester in the target RNA, the component of RISC that performs this hydrolysis is yet to be identified.

Based on the teachings of the prior and post-filing art that the components of the RISC complex are not fully known, the skilled artisan would recognize that neither the instant specification nor the knowledge in the art provide a representative sample of the genus of proteins that comprise a portion of the RISC complex. Therefore, the skilled artisan would not be able to a priori visualize the structure of the genus of proteins corresponding to the function of comprising a portion of a RNA-induced silencing complex.

Claims 62-64 are directed to methods of modulating expression of a target gene in a cell using compositions comprising two oligomeric compounds, one of which is complementary to a target nucleic acid and comprises a 4'-thionucleoside. The specification defines the term modulating on page 16 as encompassing both increase and decrease of expression. The specification provides description and working examples of oligomeric compounds that decrease expression of a target gene. The specification provides no disclosure of the structure of oligomeric compounds that increase expression of a target nucleic acid. The prior art also provides disclosure of compounds that decrease expression of target nucleic acids but does not disclose structures comprising oligomeric compounds complementary to a target nucleic that increase expression of the target nucleic acid.

In order for the written description provision of 35 USC 112, first paragraph to be satisfied, applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed. For example, MPEP 2163 states in part,

> "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.")."

The skilled artisan cannot envision the detailed structure of the encompassed oligomeric compounds that increase expression of a target nucleic acid, regardless of

the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

Therefore, the full breadth of oligomeric compounds that comprise a 4'-thionucleoside and modulate expression of a target nucleic acid encompassed by the claims and the full breadth of proteins that comprise a portion of a RNA-induced silencing complex do not meet the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant.

Claims 59-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions of oligomeric compounds comprising a pharmaceutically acceptable carrier and a method of decreasing expression of a target gene in a cell *in vitro*, does not reasonably provide enablement for pharmaceutical compositions, a method of decreasing expression of a target gene in an animal *in vivo* or for prevention of a disease in any animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples

and the quantity of experimentation needed to make the invention based on the content of the disclosure.

Claims 59-61 each recite a pharmaceutical composition. While it is accepted that claims to a composition comprising a pharmaceutically acceptable carrier do not require the composition be used as a pharmaceutical, a claim directed to a pharmaceutical composition implies the composition is to be used as a therapeutic in an organism. The instant specification does not enable use of a composition as a therapeutic in an organism as described more fully below. The rejection with regard to claims 59-61 may be overcome by removing the word "pharmaceutical" from the preamble of these claims.

Claims 62-64 are directed to methods of using compositions comprising double stranded oligomeric compounds comprising a 4'-thioribonucleoside to modulate expression of a target nucleic acid. These claims encompass methods that are performed in cells *in vitro* as well as *in vivo* in an organism. Claims 65-67 are directed to methods for the treatment or prevention of a disease associated with the expression of the target nucleic acid and have only *in vivo* embodiments.

The instant specification discloses double stranded compositions comprising 4'-thionucleosides and demonstrates that such compounds inhibit the expression of PTEN in cultured cells. The specification provides no examples of inhibition of any nucleic acid containing composition in any animal to demonstrate a therapeutic use. The specification also provides no examples where any composition is used to prevent any disease in an animal.

Problems related to therapeutic use of nucleic acids were well known in the art at the time of invention (see for example Opalinska et al. (Nature Reviews Drug Discovery,

2002, vol. 1, p. 503-514)). Such problems include the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect.

Opalinska et al. state on page 511

> "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA"

and in column 2 of the same page,

> "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in all organisms, with a resultant modulation of gene expression, as claimed. The specification provides examples of inhibition of PTEN mRNA in cultured cells, however, cell culture examples are generally not predictive of *in vivo* inhibition and the methods of delivery of the exemplified cell line would not be applicable to delivery of oligonucleotides to any organism. Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results. Given these teachings, the skilled artisan would not know *a priori* whether introduction of oligonucleotides *in vivo* by the broadly disclosed methodologies of the instant invention, would result in the oligonucleotide reaching the proper cell in a sufficient concentration and remaining for a sufficient time to provide successful inhibition of

expression of a target gene. In fact, the state of the art is such that successful delivery of oligonucleotide sequences *in vivo* or *in vitro*, such that the polynucleotide or oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically.

In addition to treatment of disease, claims 65-67 are directed to methods of prevention of disease. To prevent a pathological condition means to keep this condition from occurring. Using cancer as an example, to prevent cancer means to keep cancer from occurring in a subject now or in the future. Cancer is a generic term for more than 100 diseases characterized by uncontrolled, abnormal growth of cells. The state of the prior art does not consider cancer to be preventable and recognizes (see Bocchetta et al. 2004) that:

> "Cancer is a multifactorial event in which numerous alterations contribute to the emergence of the malignant cell...therefore, malignant tumor growth is a dynamic process in which it is difficult to identify a unique event that caused that process".

Given the known difficulty in identifying the particular events that cause the process of cancer and a reasonable interpretation of prevention, one of skill in the art would conclude that no method known currently will prevent from happening in a subject, now or at any future time, the more than 100 diseases encompassed by the term cancer.

The specification describes the use of double stranded nucleic acids to inhibit expression of PTEN in cultured cells, but does not provide any specific guidance of how to use these compounds to prevent any disease and provides no examples of prevention of any disease using the oligomeric compounds of the invention.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of using nucleic acids in therapeutic applications in any

organism. The teachings of the prior art do not provide that guidance, such that the skilled artisan would be able to practice the claimed therapeutic methods.

Thus, while the specification is enabling for the examples set forth in the specification, the specification is not enabling for the broad claims of modulating the expression of a target nucleic acid or preventing any disease in any organism as the art of inhibiting gene expression by introducing nucleic acids into an organism is neither routine nor predictable. Because no specific method of preventing any disease is disclosed in the specification, the skilled artisan would have to perform a large and undue quantity of trial and error experimentation in order to determine how to prevent a disease associated with expression of any target nucleic acid using the double stranded oligomeric compounds of the invention. In addition, to practice the instant invention, the skilled artisan would be required to monitor any subject for the remainder of their lifetime to ensure that the modulator of the invention indeed prevented the disease from happening in said subject. In this case, the quantity of trial and error experimentation required to determine that a method would actually prevent disease and the lack of guidance in the specification regarding the direction in which the experimentation should proceed demonstrate that the instant invention is not enabled for prevention of any disease. The amount of experimentation required is such that one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 59-67 are not enabled.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10, 12, 25, 53-59, 61, 62 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al. (WO 94/01550, cited on IDS of 4/4/05) in view of Barascut et al. (US 5,639,873, cited on IDS of 4/5/04).

The claimed invention is directed to oligomeric compounds capable of hybridizing to a target nucleic acid comprising single strands with a portion of self-complementarity or two complementary strands and further comprising at least one 4'-thionucleoside. In specific embodiments the oligomers are a pair of siRNA oligomers or a pair of sense/antisense oligomers that are 10-40, 18-30 or 21-24 nucleotides in length. The

single stranded oligomers can further comprise a third region of nucleotides or non-nucleotides. The claimed invention is also directed to methods of modulating expression of a target nucleic acid by administering these oligomeric compounds to a cell.

Agrawal et al. teach self-stabilized oligonucleotides comprising a target hybridizing region and a self-complementary region. The oligonucleotides can comprise deoxyribonucleotides, ribonucleotides, or a combination thereof. On page 15 Agrawal et al. teach that the self-complementary region of the oligonucleotide is fully or partially complementary to the hybridizing region while at page 9, line 30 through page 10 line 1 it is taught that the target hybridizing region comprises 8 to 50 nucleotides and is complementary to a nucleic acid sequence from a variety of sources including viruses, pathogens, cellular genes or gene transcripts. Pages 15 and 16 describe embodiments where the oligonucleotide is a single nucleic acid strand that forms a double stranded structure as well as an embodiment where the self-complementary region is connected to the hybridizing region by a non-nucleotide linker, making the self-complementary region and the hybridizing region two separate complementary nucleic acid strands. On pages 17, line 27 through page 18 Agrawal et al. teach that the self-stabilized oligonucleotides can be administered to the cells of an animal to inhibit gene expression in the animal and treat disease. Agrawal et al. exemplify this embodiment in cultured cells. At page 16, Agrawal et al. teach that the oligonucleotides of their invention comprise nucleotide modifications that enhance nuclease resistance and/or cellular uptake and/or affinity of the oligonucleotide for its target. Agrawal et al. do not explicitly teach the use of 4'-thionucleosides as a nucleotide modification.

It was well known in the art at the time of invention that sugar modified nucleosides are useful for stabilization of therapeutic nucleic acids. Barascut et al. teach one such sugar-modified nucleoside in the form of 4'-thionucleosides, a sugar modified nucleoside where the furanose oxygen is substituted with sulfur. At column 2, lines 47-64 Barascut et al. teach that oligonucleotides comprising 4'-thionucleosides in either the ribonucleotide or deoxyribonucleotide forms have increased solubility and stability as compared with oligonucleotides without the modified sugar. Barascut et al. also suggest that such oligonucleotides would have increased cellular uptake due to the increased lipophilic character of the sulfur substitution.

It would have been obvious to one of ordinary skill in the art at the time of invention to make the self-stabilized oligonucleotides taught by Agrawal et al. with the 4'-thionucleosides taught by Barascut et al. It would have been further obvious to use these oligonucleotides to decrease expression of a target nucleic acid in a cell. Agrawal et al. provide a motivation to make self-stabilized oligonucleotides with nucleotide modifications by explicitly suggesting such modifications and provide a motivation to use these oligonucleotides to inhibit gene expression by both suggesting and exemplifying such use. Barascut et al. provide a motivation to make an oligonucleotide comprising 4'-thionucleosides by teaching that such substitution provides an oligonucleotide with increased solubility and increased stability due to increased affinity for a target nucleic acid. One of ordinary skill in the art would have had a reasonable expectation of success in combining the teachings of Agrawal et al. and Barascut et al. because methods of producing modified oligonucleotides are well-known and routinely

used in the art and because methods of inhibiting gene expression using such oligonucleotides are also well-known in the art.

Thus, the invention of claims 1-10, 12, 25, 53-59, 61, 62 and 64 would have been obvious, as a whole, at the time of invention.

Claims 1-10, 12, 25, 28-35, 37 and 53-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. (US 2004/0029275) in view of Barascut et al.

The claimed invention is directed to oligomeric compounds capable of hybridizing to a target nucleic acid comprising single strands with a portion of self-complementarity or two complementary strands and further comprising at least one 4'-thionucleoside. In specific embodiments the oligomers are a pair of siRNA oligomers of a pair of sense/antisense oligomers that are 10-40, 18-30 or 21-24 nucleotides in length. The single stranded oligomers can further comprise a third region of nucleotides or non-nucleotides or further comprises a protein comprising a portion of a RNA-induced silencing complex (RISC). The claimed invention is also directed to methods of modulating expression of a target nucleic acid by administering these oligomeric compounds to a cell.

Brown et al. teach siRNAs and methods of using these siRNAs to inhibit gene expression. At paragraphs 21-22, Brown et al. teach that the siRNAs can be 15-1000 nucleotides in length and can comprise one or two strands, while at paragraph 18 Brown et al. teach that the siRNAs of the invention associate with the RISC which includes formation of a composition comprising a siRNA and a protein comprising a portion of a RNA induced silencing complex. At paragraph 152 they teach the siRNAs

of the invention comprise modified nucleotides that include derivatives or analogs of 5 carbon sugars. Brown et al. do not explicitly teach that their siRNAs comprise 4'-thionucleosides.

It was well known in the art at the time of invention that sugar-modified nucleosides are useful for stabilization of therapeutic nucleic acids. Barascut et al. teach one such sugar-modified nucleoside in the form of 4'-thionucleosides, a sugar-modified nucleoside where the furanose oxygen is substituted with sulfur. At column 2, lines 47-64 Barascut et al. teach that oligonucleotides comprising 4'-thionucleosides in either the ribonucleotide or deoxyribonucleotide forms have increased solubility and stability as compared with oligonucleotides without the modified sugar. Barascut et al. also suggest that such oligonucleotides would have increased cellular uptake due to the increased lipophilic character of the sulfur substitution.

It would have been obvious to one of ordinary skill in the art at the time of invention to make the siRNAs comprising modified nucleotides taught by Brown et al. with the 4'-thionucleosides taught by Barascut et al. It would have been further obvious to use these oligonucleotides to decrease expression of a target nucleic acid in a cell. Brown et al. provide a motivation to make siRNAs with nucleotide modifications by explicitly suggesting such modifications and provide a motivation to use these oligonucleotides to inhibit gene expression by both suggesting and exemplifying such use. Barascut et al. provide a motivation to make an oligonucleotide comprising 4'-thionucleosides by teaching that such substitution provides an oligonucleotide with increased solubility and increased stability due to increased affinity for a target nucleic acid. One of ordinary skill in the art would have had a reasonable expectation of

success in combining the teachings of Brown et al. and Barascut et al. because methods of producing modified oligonucleotides are well-known and routinely used in the art and because methods of inhibiting gene expression using such oligonucleotides are also well-known in the art.

Thus, the invention of claims 1-10, 12, 25, 28-35, 37 and 53-64 would have been obvious, as a whole, at the time of invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The central FAX Number is 571-273-8300.

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TV
September 25, 2006

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER